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EXAMINER	
LANDSMAN, ROBERT S	
ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/835,995	Applicant(s) SODERBERG ET AL.	
	Examiner Robert Landsman	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-79* is/are pending in the application.

4a) Of the above claim(s) *1-29 and 36-79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-35* is/are rejected.

7)☒ Claim(s) *30-35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,9,10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Comparison* .

DETAILED ACTION

1. Formal Matters

A. Claims 1-79 are pending in the application and were subject to restriction in Paper No. 8, dated 4/11/02. In the response dated 10/11/02, Applicants elected Group II, claims 30-35. Applicants argue that no serious burden would be imposed in performing a search of several Groups. However, for the reasons provided in the restriction dated 4/11/02, reciting that the products and methods are independent and distinct, the restriction is deemed proper and is, therefore, made FINAL.

B. The Supplemental Information Disclosure Statement, filed 1/18/02, has been entered into the record.

C. The Supplemental Information Disclosure Statement, filed 6/19/02, has been entered into the record.

D. The Supplemental Information Disclosure Statement, filed 9/3/02, has been entered into the record.

2. Information Disclosure Statement

A. . A Paper was filed 7/5/01, stating that an Information Disclosure Statement has been filed. This Paper has been entered into the record. However, no Form PTO-1449 accompanies this Paper. Therefore, the references cited on this IDS have not been considered by the Examiner.

B. Reference AD on the Form PTO-1449, filed 1/18/02, has been lined through since a PCT International Search Report is not proper subject matter for an IDS.

3. Claim Objections

A. Claims 30-35 are objected to since they directly, or ultimately, depend from non-elected claim 1.

4. Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

A. Claims 30-35 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility. These claims are directed to a protein of SEQ ID NO:2. However, the invention encompassed by these claims has no apparent or disclosed patentable utility. This rejection is consistent with the current utility guidelines, published 1/5/01, 66 FR 1092. The instant application has provided a description of an isolated protein. However, the instant application does not disclose a specific and substantial biological role of this protein or its significance.

However, it is clear from the instant specification that the claimed receptor is what is termed an "orphan receptor" in the art. The instant application does not disclose the biological role of the claimed protein or its significance. Applicants disclose in the specification that the claimed receptor is believed to be a G protein-coupled receptor. However, the basis that the receptor of the present invention is a 7 transmembrane receptor is not predictive of a use. There is little doubt that, after complete characterization, this protein will probably be found to have a patentable utility. This further characterization, however, is part of the act of invention and, until it has been undertaken, Applicants' claimed invention is incomplete.

The instant situation is directly analogous to that of which was addressed in Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. 101, which required that an invention must have either an immediate obvious or fully disclosed "real-world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility," "[u]nless and until a process is refined and developed to this point - where specific benefit exists in currently available form – there is insufficient justification for permitting an applicant to engross what may prove to be a broad field," and "a patent is not a hunting license," "[i]t is not a reward for the search, but compensation for its successful conclusion."

The specification discloses that the protein of the invention encode proteins which is homologous to G protein-coupled receptors. Based on the structural similarity, the specification asserts that the newly disclosed SEQ ID NO:2 has similar activities. The assertion that the disclosed proteins have biological activities similar to known G protein-coupled receptors cannot be accepted in the absence of supporting evidence, because generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene.

Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan the utility of the claimed protein of SEQ ID NO:2 which is only known to be homologous to G protein-coupled receptors. Therefore, the instant claims are drawn to a protein which has a yet undetermined function or biological significance. There is no actual and specific significance which can be attributed to said protein identified in the specification. For this reason, the instant invention is incomplete. In the absence of a knowledge of the natural ligands or biological significance of this protein, there is no

immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which bind to and/or mediate activity of the said receptor is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real-world" use for said protein then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. 101 as being useful.

5. Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 30-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to use the instant invention. Specifically, since the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

6. Claim Rejections - 35 USC § 112, first paragraph – scope of enablement

A. Furthermore, even if the claims possessed utility under 35 USC 101, claim 33 would still be rejected under 35 USC 112, first paragraph, because the specification, while then being enabling for the polypeptide of SEQ ID NO:2, does not reasonably provide enablement for a polypeptide of SEQ ID NO:2 having at least one conservative amino acid substitution. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to *** the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

First, the breadth of the claims is excessive regarding all proteins which have at least one conservative amino acid substitution to the protein of SEQ ID NO:2. In theory, these proteins could have every amino acid in the protein altered. Applicants have not provided any guidance or working examples of what changes could be made to the protein of SEQ ID NO:2 and which would not alter the funcion of SEQ ID NO:2, especially given that this protein is an orphan with no specific disclosed function as

discussed in the above rejection under 35 USC 101. Similarly, it is not predictable to one of ordinary skill in the art which amino acid residues to alter in order to maintain the function of SEQ ID NO:2, especially, but not solely, given the fact that there is no functional limitation recited in the claims.

Therefore, due to this excessive breadth, lack of guidance and working examples, as well as the unpredictability as to what residues of SEQ ID NO:2 can be altered and still retain the function of the protein of SEQ ID NO:2, the Examiner holds that undue experimentation would be necessary to practice the claimed invention.

B. Claims 34 and 35 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims include in scope allelic variants of the disclosed protein of SEQ ID NO:2. In the absence of a definition of "allelic variant" in the specification, the Examiner notes that the implied definition in claim 34 is at odds with the art accepted meaning of allelic variant, since the definition of "allele" is drawn exclusively to the state of a gene itself, and has no direct connotation regarding the protein encoded by the gene (it is noted that even genes or sequences which do not encode protein may exist as alleles). For example, Ayala and Kiger (Modern Genetics, Benjamin/Cumings 1980) define allele as "One of two or more alternative forms of a gene, each possessing a unique nucleotide sequence; different alleles of a given gene are usually recognized, however, by the phenotypes rather than by comparison of their nucleotide sequences." Thus, while allelic genes may result in a phenotypic change, the word does not have any particular connotation as to the encoded protein. Given this, the Examiner cannot determine how one would distinguish, merely by examination of the protein, whether a protein were the result of expression of a different allele. In addition, enablement is not commensurate in scope with claims to proteins encoded by allelic variants of the disclosed sequences. The specification discloses the claimed protein, and, hence, its variants, to be useful for their biological activity. However, allelic variants often encode proteins with quantitatively or qualitatively altered or absent biological activity. Therefore, the specification does not teach how to use such variants, nor is adequate guidance provided for the skilled artisan to predict, *a priori*, which variants would reasonably be expected to retain biological function. Claim 35 is rejected since it depends from claim 34.

7. Claim Rejections - 35 USC § 112, first paragraph – written description

A. Claims 34 and 35 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:2 and, therefore, the written description is not commensurate in scope with the claims drawn to allelic variants of SEQ ID NO:2

Claim 34 is drawn to the genus including all allelic variants of SEQ ID NO:2. The specification does not provide any particular definition for the term 'allele.' In this circumstance, the meaning of the term is the ordinary usage in the art. The ordinary meaning of the term 'allele' is one of two or more alternate forms of a gene occupying the same locus in a particular chromosome or linkage structure and differing from other alleles of the locus at one or more mutational sites. See, Rieger et al., *Glossary of Genetics* (1991), p. 16. The Rieger et al. reference discloses that there are at least seven different kinds of alleles in addition to the 'strictly neutral' type discussed above for claims 26-29. See Rieger, pp 16-17 (amorphs, hypomorphs, hypermorphs, antimorphs, neomorphs, isoalleles and unstable alleles). The alleles are distinguished by the effect their different structures have on phenotype. According to Rieger et al., alleles may differ functionally according to their distinct structures. For example, they may differ in the amount of biological activity the protein product may have, in the amount of protein produced, and/or the kind of activity the protein product will have.

Thus, the structure of allelic sequences are not defined. With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

The specification discloses only one allele encoding the protein within the scope of the genus: SEQ ID NO:1 for the protein of SEQ ID NO:2. There is no description of the mutational sites that exist in nature, and there is no description of how the structure of the DNA encoding the claimed "allelic variants" relates to the structure of different alleles. In addition, according to the standard definition, the genus includes members that would be expected to have widely divergent functional properties. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of other unknown alleles having concordant or discordant functions. The

common attributes of the genus are not described and the identifying attributes of individual alleles, other than SEQ ID NO:1 are not described. The nature of alleles is that they are variant structures where the structure of one does not provide guidance to the structure and function of others. According to these facts, one of skill in the art would conclude that the Applicant was not in possession of the claimed genus because a description of only one member of the genus is not representative of the variants of the genus and is insufficient to support the claim.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Furthermore, In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

No disclosure, beyond the mere mention of allelic variants is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guildlines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645. Therefore only an isolated DNA molecule comprising a DNA sequence consisting of SEQ ID NO:1 and equivalent degenerative codon sequences thereof, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

8. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claims 34 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "allelic variant" vague and indefinite for the reasons in the above rejection under 35 USC 112, first paragraph, under scope of enablement.

B. Claim 32 is confusing since it recites that the polypeptide is "homologous" to SEQ ID NO:2. The paragraph bridging pages 7 and 8 state that a homologous protein has the specified percentage of similarity to a protein of the invention. However, no percentage is recited in the claim. Therefore, a homologous protein could be interpreted as a protein which is 100% identical to SEQ ID NO:2, making claim 32 fail to further limit claim 30.

9. Closest Prior Art

A. Bonaldo et al. teach a polynucleotide encoding a protein which is 44% identical to SEQ ID NO :2 of the present invention.

10. Conclusion

A. No claim is allowable.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
November 13, 2002